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09/478,263	01/05/2000	KEVIN A. JARRELL	0342941-0043	1459

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/478,263	Applicant(s) JARRELL ET AL.	
File Copy	Examiner Jon D Epperson	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on May 6, 2003 (Paper No. 19).

Priority Claims

2. The priority filing date of January 5, 1999 for application 60/114,909 is acknowledged.

Status of the Claims

3. Claims 1-3 and 5-21 are pending in the present application.

4. Regarding the election of species, the following is noted. MPEP § 803.02 (cited in part):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

Applicant's claims were first searched to the extent of the elected species. No art was found, thus the search was extended. The art search was extended to all species and no prior art

was found that anticipates or renders obvious the instant claims. However, the rejections below apply to the claims.

5. Therefore, claims 1-3 and 5-21 are examined on the merits in this action.

Response to Restriction and/or Election of Species

6. Applicant's election of species in Paper No. 19 with traverse is also acknowledged.

7. The election of species traversal is on the ground(s) that the Examiner would not be unduly burdened based on a preliminary search of the literature by Applicants (see Paper No. 19, page 1).

8. These arguments were fully considered but were not found persuasive. As stated previously in Paper No. 17, the different species would require different searches and there is no expectation that the searches would be coextensive. The examiner maintains that this does create an undue search burden. The fact that Applicants did a search is simply not relevant. The Examiner is responsible for the search not Applicants.

9. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

10. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

11. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-3 and 5-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

These claims encompass a broad genus. For example, claim 1 outlines steps for combinatorial biosynthesis using only generic language like "starter units", "handles", "solid supports", "biosynthetic enzymatic machinery systems" and "organic synthesis" to produce a library of products including intermediate "template structures" and final "unnatural natural products." The scope of this claim includes an infinite number of methods for producing and/or using an infinite number of "template structures", "unnatural natural products", "starter units", "handles", "solid supports", "antibody recognition units", etc. wherein no distinguishing structural attributes (i.e., no representative examples) are provided for any of the said reagents and/or products. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form these reagents and products. In addition, the claims would also include an infinite number of enzymes (including enzymes derived from an undetermined number of unrelated metabolic pathways) including "modified" enzymes (e.g., chemical, radiation, genetic, etc. mutations) and also an infinite number chemical functionalities generated by the

"functionalization" of intermediate template products via "organic chemistry" (i.e., presumably including all the chemical reactions ever created over time).

In contrast to Applicants enormous claimed scope, Applicants' specification does not even provide a single working example of this method with any specificity (no *quid pro quo*). For example, the specification does not disclose a single "representative" example of a "support bound starter unit", "template structure", "species of template structure after functionalization", "nonnatural natural product", "antibody recognition element" (e.g., see Applicants' response, Paper No. 19, page 2, "Applicants have not specified any species of solid support unit through out the specification and the claims"; see also page 3, paragraph 1, "Applicants have not indicated in the specification or claims any species of template"; see also page 3, paragraph 4, "Applicants have not indicated in the specification or claims any particular species of template after functionalization"; see also page 4, last paragraph, "Applicants have not indicated in the specification or claims any particular species of nonnatural natural product") and, as a result, the specification and claims do not provide ***ANY*** guidance as to what structural features ***all*** of these reagents and products share. Consequently, it is not possible to determine *a priori* which reagents and products would be encompassed by Applicants' broad claims because there is no common structural attributes that can link together ***all*** of these potential reagents and products i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of compounds that should be included in this genus from the complete lack of working examples in the specification.

With respect to adequate disclosure applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires ***representative examples*** which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that ***applicant had possession of the full scope of the claimed invention***. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description (i.e., Applicants' generic language) because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, using only generic terminology without specific examples (see above) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

14. Claims 1-3 and 5-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for ***any*** of Applicants' currently claimed embodiments. Applicants have not provided ***any*** examples of a solid support unit (see Paper No. 19, page 2, "Applicants have not specified any species of solid support unit") that is critical to ***all*** of Applicants' currently claimed embodiments and, as a result, a person of skill in the art would not know how to practice the claimed invention without undue experimentation. This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to a broad genus. For example, claim 1 outlines steps for combinatorial biosynthesis using only generic language like "starter units", "handles", "solid supports", "biosynthetic enzymatic machinery systems" and "organic synthesis" to produce a library of products including intermediate "template structures" and final "unnatural natural

products." The scope of this claim includes an infinite number of methods for producing and/or using an infinite number of "template structures", "unnatural natural products", "starter units", "handles", "solid supports", "antibody recognition units", etc. wherein no distinguishing structural attributes (i.e., no representative examples) are provided for any of the said reagents and/or products. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form these reagents and products. In addition, the claims would also include an infinite number of enzymes (including enzymes derived from an undetermined number of unrelated metabolic pathways) including "modified" enzymes (e.g., chemical, radiation, genetic, etc. mutations) and also an infinite number chemical functionalities generated by the "functionalization" of intermediate template products via "organic chemistry" (i.e., presumably including all the chemical reactions ever created over time). Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: While combinatorial biosynthesis has been known for some time, there are no examples of "solid phase" combinatorial biosynthesis. Therefore, the Examiner contends that the level of predictability in the art is low or absent.

A person of skill in the art would not know how to place a "support bound starter unit" inside a host cell in such a way as to insure its interaction with the host "biosynthetic enzymatic machinery" without at least one example from Applicants (there are no examples of this in the literature). Furthermore, a person of skill in the art would

not know how to pick "solid supports" that would insure a reaction between a "biosynthetic enzymatic machinery system" and the "support bound starter units" (there are no examples of this in the literature). While the art shows that in some cases the "biosynthetic enzymatic machinery" has relaxed specificity and thus could accommodate a wider array of substrates, it does not show that the enzymes could accommodate substrates on a solid support like a bead or a chip (which would fall within the scope of Applicants' claims). How would a "support bound starter unit" get transferred from one enzyme to the next in the modular biosynthetic enzymatic machinery when it is bound to a reaction bead?

Furthermore, combinatorial biosynthesis is a new and highly unpredictable field that requires identification/characterization of the "modular biosynthetic enzymatic machinery." With the exception of polyketides and nonribosomally produced peptides and carbohydrates, this has not been done. For example, Taylor states that for the biosynthesis of epothione would require a mixed NRPS/PKS "biosynthetic enzymatic machinery." However, Taylor states that there are currently "no examples of such an approach [in the literature]" and that while it may be "easy to imagine how novel epothione analogs could be generated", "[m]uch work remains to be done in elucidating the organization and structure of hybrid PKSs/NRPSs, however, before combinatorial biosynthesis with these systems can be undertaken" (emphasis added) (see Taylor, S. V. in "Handbook of Combinatorial Chemistry" Eds. Nicolaou, K. C.; Hanko, R.; Hartwig, W. Weinheim Germany: Wiley-VCH 2002, Vol. 2, page 1075, last paragraph).

Therefore, Applicants are clearly not enabled for systems like PKS/NRPS wherein the "biosynthetic enzymatic machinery" has not yet been characterized.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided a single working example of this method with any specificity. For example, the specification does not disclose reagents and products that are essential for the method including examples of a "support bound starter unit", "template structure", "species of template structure after functionalization", "nonnatural natural product", "antibody recognition element" (e.g., see Applicants' response, Paper No. 19, page 2, "Applicants have not specified any species of solid support unit through out the specification and the claims"; see also page 3, paragraph 1, "Applicants have not indicated in the specification or claims any species of template"; see also page 3, paragraph 4, "Applicants have not indicated in the specification or claims any particular species of template after functionalization"; see also page 4, last paragraph, "Applicants have not indicated in the specification or claims any particular species of nonnatural natural product") (emphasis added).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples

or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-3 and 5-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. ***Claims 1, 3, 8 and 14*** are rejected because the "starter units" in these claims are not defined with any chemical or physical characteristic, but only by functional properties i.e., their ability to act as substrates for one or more biosynthetic enzymes. A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot

immediately envision all the possible chemical structures for a peptide with this function. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169. Therefore claims 1, 3, 8 and 14 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. ***Claims 1, 3 and 7*** are rejected because the "handle[s]" in these claims are not defined with any chemical or physical characteristic, but only by functional properties i.e., their ability to function as a linker to a solid support. A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a peptide with this function. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169. Therefore claims 1, 3 and 7 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. **Claim 3** recites the limitation "collection of structures" in step (d). There is insufficient antecedent basis for this limitation in the claim. The Examiner recommends "collection of template structures." Therefore, claim 3 and all dependent claims are rejected under 35 U.S.C 112, second paragraph.

D. ***Claim 7*** recites "chemically robust functionality" in line 1-2. The term "robust" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of

the scope of the invention. Therefore, claim 7 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

E. ***Claims 11-13*** recite "modified enzymes" in line 1-2. The term "modified" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore, claim 11 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

F. ***Claims 14 and 15*** are rejected because the "antibody recognition elements" in these claims are not defined with any chemical or physical characteristic, but only by functional properties i.e., their ability to bind to antibodies. A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a peptide with this function. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169. Therefore claims 14, 15 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Contact Information

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
July 27, 2003

BENNETT CELSA
PRIMARY EXAMINER